REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-283 are in this case. Claims 1-12, 65-96 and 101-283 have been withdrawn as being drawn to non-elected invention. Claims 13-64 and 97-100 have been rejected. Claims 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 53, 54, 57, 58, 61, 62, 97, and 98 have now been amended. New claims 284-297 have been added.

Election/Restrictions

The Examiner has pointed out that the required election of a specific sequence (SEQ ID NO:4) is not a species selection, asserting that "the peptide sequences set forth in the claims of the invention are structurally (in both composition and sequence) distinct/different from one another, and thus [they] patently distinct..." (see page 2, second paragraph of the DETAILED ACTION mailed June 30, 2005). It is Applicant's strong opinion that the Examiner is incorrect in this assertion, and that the peptide sequences set forth the instant specification represent overlapping peptides having greatly similar composition, sequence and function, and should be considered as individual species belonging to the genus of peptides derived from α S1 casein.

Applicant wishes to point out that the peptide sequences as set forth in SEQ ID NOs: 1-25 represent 25 sequential overlapping peptides, having sequences representing the first two N-terminal amino acids of α S1 casein (SEQ. ID NO:1), the first three N-terminal amino acids of α S1 casein (SEQ ID NO:2), the first four N terminal amino acids of α S1 casein (SEQ ID NO:3), and so on, up to and including the first 26 N terminal amino acids of α S1 casein (SEQ ID NO:25) (see Table 3, pages 58 and 59 of the instant specification). Thus, in contrast to the Examiner's assertion that the peptide sequences set forth in the claims are distinct in composition and sequence from one another, Applicant is of the strong opinion that the sequential overlapping peptides of SEQ ID NOs: 1-25 represent individual species of a single genus, having significant identity of sequence and composition.

In illustration, applicant wishes to refer the Examiner to page 9, third paragraph of the DETAILED ACTION mailed June 30, 2005, in which the Examiner asserts the essential patentable identity of the bovine α S1 casein peptide fragment 16-53, as

described by Enomoto et al (Mol Immunol 1990;27:581-586) with SEQ ID NO:4 of the instant specification:

"Because structural feature is inherent property of a biomolecule, the said α S1 casein peptide (i.e. fragment 16-53) would have the abovementioned biological activities. It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties discloses and/or claims are necessarily present."

Thus, by the same criteria, the sequential overlapping peptides as set forth in SEQ ID NOs: 1-25, having far greater identity of composition and sequence than the peptide disclosed by Enomoto et al, are clearly not patentably distinct, and would be expected to share the abovementioned biological properties, and as such, should rightly be regarded as individual species of the single genus of peptides derived from the N terminal portion of α S1 casein.

Further, Applicant wishes to emphasize, (as has been noted by the Examiner on page 2 of the DETAILED ACTION mailed June 30, 2005, second paragraph), that when responding to the restriction requirement in this case (communication of July 1, 2004), Applicant was under the impression that Applicant is selecting a species and not electing an invention, as is clearly evident from the text of the response to the restriction requirement, dated September 28, 2004 and filed on February 2, 2005.

In view of the Examiner's stated position on the criteria for determining patentable distinction between members of a genus of N terminal α S1 casein peptides, Applicants respectfully request reclassification of the election of SEQ ID NO: 4 as a species selection, and continuing examination accordingly.

Specification/Claim Objections

The Examiner has objected to the disclosure due to the following informalities:

(1) FITC (page 21), RPE (page 21) and BSA (page 62) should be spelled out in full for the first instance of use. The indicated paragraphs have been amended accordingly (see above).

(2) Drawings: Tables in Figures 2a, 3a, 3b, 3c , 4, 5a, 8, 9, 11 and 15 are not appropriately labeled. Amended drawings including Figures 2a, 3a, 3b, 3c, 4, 5a, 8 and 9 are enclosed herein. Specifically:

FIG. 2a: The Examiner has stated that the Table above the plot is inappropriately labeled. The table above the plot has now been deleted. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

FIGs. 3a-3c: The Examiner has stated that the Tables above the plot are inappropriately labeled. The Tables above the plot have now been labeled to recite "Peptides derived from natural casein" in place of "CHAY-13". The control and experimental values are now clearly indicated. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

FIG. 4: The Examiner has stated that the Table above the plot is inappropriately labeled. The Table above the plot has now been labeled to recite "Synthetic Peptides derived from natural casein" in place of "CHAY-13". The identity of the peptides is clearly indicated. The control and experimental values are now clearly indicated. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

FIG. 5a: The Examiner has stated that the Table to the left of the plot is inappropriately labeled. The Table to the left of the plot has now been labeled to clearly indicate the control and experimental treatments administered to the cells, and their response to treatment. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

FIG. 8: The Examiner has stated that the Table above the plot is inappropriately labeled. The Table above the plot has now been deleted. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

FIG. 9: The Examiner has stated that the Table above the plot is inappropriately labeled. The Table to above the plot has now been labeled to recite "Peptides derived

from natural casein" in place of "CHAY-13". The control and experimental values are now clearly indicated. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

FIG. 11: The Examiner has stated that FIG. 11 comprises two Tables, and that the bottom Table should be labeled. Applicant wishes to point out that FIG. 11 does not have two separate Tables, but rather contains upper and lower sections of a single Table entitled "Stimulation of Sup-T_1 Lymphocyte Cell Proliferation by Peptides Derived from Natural Casein", with 4 separate columns relating to the results of 3 days and 7 days (upper panel), and 10 days and 14 days (lower panel) treatment. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

FIG. 15: The Examiner has stated that FIG. 15 comprises two Tables, and that they should be labeled. Applicant wishes to point out that FIG. 15 does not have two separate Tables, but rather contains upper and lower sections of a single Table entitled "Total Cholesterol (TC), LDL & HDL levels in Hypercholesterolemic/Hyperlipidemic C57 Bl/6J", with an upper panel indicating individual test results for each sample, and a lower panel labeled "MEAN VALUES" indicating the averages for each group. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

FIGs. 17 and 18: The Examiner has stated that the meaning of the X and Y values in the Tables above the plots are unclear. The Tables above the plot has now been deleted. Further descriptive details are found in the "Brief Description of Drawings" section of the instant specification.

(3) The definition for "oS1 casein" is unclear. Applicant regrets the unexpected technical error leading to such lack of clarity in this matter. As the Examiner has noted, from both other applications filed by the Applicant, and from the peptide sequences identified in the present specification (see, for example, SEQ ID NO: 15, as compared to amino acids 1-23 of the N-terminal portion of αS1 casein, NP 851372:casein alpha-S1), "oS1 casein" and "αS1 casein" are indeed the same composition. Applicant regrets the confusion, and respectfully requests that any reference to "oS1 casein" made throughout the entire specification be read as "αS1 casein" instead.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 13-64 and 97-100 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 53, 54, 57, 58, 61, 62, 97, and 98 have now been amended. New claims 284-297 have been added.

The Examiner has stated that the specification does not describe the amino acid sequence of full length oS1 casein, nor sufficiently describes the N-terminal portion thereof, nor the core sequence(s) or structural motifs which are important for the biological activity of the N-terminal portion peptide of oS1 casein, e.g. plasma cell proliferation.

Applicant regrets the unnecessary confusion associated with the typographical error in the designation of αS1 casein in the instant specification, and believes that the relevant comments and explanations provided hereinabove [see ***Specification/Claim Objections,*** item (3)] have now clarified the identity of "oS1 casein" as "αS1 casein". Specifically, the Examiner has stated that the specification does not describe the full length amino acid sequence of the "oS1 casein" (αS1 casein). Applicant wishes to point out that the full length sequence of αS1 casein is disclosed in the instant specification: "As used herein the term "αS1 casein" refers to αS1 casein of a mammal, including, but not limited to, livestock mammals (e.g., cow, sheep, goat, mare, camel, deer and buffalo) human beings and marine mammals. The following provides a list of αS1 caseins having a known amino acid sequence, identified by their GenBank (NCBI) Accession Nos. and source: CAA26982 (*Ovis aries* (sheep)), CAA51022 (*Capra hircus* (goat)), CAA42516 (*Bos taurus* (bovine)), CAA55185 (*Homo sapiens*), CAA38717 (*Sus scrofa* (pig)), P09115 (rabbit) and O97943 (*Camelus dromedurius* (camel))" (page 35, lines 1-9).

The Examiner has further stated that the specification does not sufficiently describe the N-terminal portion of "oS1 casein". Regarding the N-terminus portion of "oS1 casein" (αS1 casein), Applicant wishes to point out that the term "N-terminus portion" of αS1 casein is also clearly defined in the instant specification:

"As used herein the term "N terminus portion" refers to M amino acids of αS1 casein derived from the first 60 amino acids of αS1 casein, wherein M is any of the integers between 2 and 60 (including the integers 2 and 60). Preferably, the term refers to the first M amino acids of αS1 casein" (page 35, lines 10-13).

Thus, Applicant believes that one skilled in the art would recognize, and know how to make and use the N-terminal portion of αS1 casein in order to practice the claimed invention.

The Examiner has stated that the interspecies variety in peptide sequences of αS1 casein would cause one of ordinary skill in the art to be unable to make and use the N terminal portion of the αS1 casein ("oS1 casein") to develop the methods of claims 13-64, and 97-100. Applicant wishes to reiterate that the amino acid sequences of αS1 casein from various mammalian species are well known in the art, and are easily obtained from publicly available databases. Further, Genebank accession numbers of the αS1 casein sequences from sheep, goat, bovine, pig, rabbit, human, camel, etc., known at the time of the invention, are disclosed in the instant specification (see above), and expressly incorporated in their entirety therein:

"All publications, patents, patent applications and sequences identified by an accession number, mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent, patent application or sequence was specifically and individually indicated to be incorporated herein by reference."(page 97, lines 3-7, of the instant specification).

Thus, one of ordinary skill in the art would readily identify, and be capable of using the N terminus portion of any of the claimed αS1 casein sequences in order to develop the methods of the present invention as claimed.

The Examiner has stated that the specification does not describe methods of preventing thrombocytopenia, pancytopenia or/and granulocytopenia comprising administering to a subject a peptide comprising the N-terminal portion of αS1 casein. Applicant wishes to point out that methods for administration of therapeutically effective doses of peptides from the N-terminal portion of αS1 casein are described in detail in the instant specification, including numerous formulations and pharmaceutical compositions, modes of application and methods for determining therapeutically effective doses from

in-vitro and *in-vivo* data (pages 36-40). Further, Applicant wishes to point out that the instant specification discloses numerous examples of the hematopoietic effects of peptides of the N-terminal portion of αS1 casein in *in-vitro* models of various hematopoietic cell proliferation, as well as the *in-vivo* enhancement of bone marrow engraftment and stimulation of platelet, leukocyte regeneration in myelodepleted hosts. In particular, the Examples section of the instant specification discloses stimulation of murine and human NK and T cell proliferation in bone marrow and peripheral blood stem cell cultures (pages 74-77, 84-85); stimulation of proliferation of ALL hematopoietic progenitors from cultured bone marrow, cord blood and peripheral blood (pages 77-78), increased megakaryocyte production (CFU-GM and CFU-GEMM) in bone marrow cultures (pages 77-78), and increased dendritic cells, plasma cells, macrophage proliferation, RBC and PMN proliferation (pages 81-82) following exposure to the N-terminal portion of αS1 casein. Reconstitution of bone marrow in irradiated hosts, with cells from donors treated with the N-terminal portion of αS1 casein, leading to superior host survival was disclosed (page 74). Further, *in-vivo* administration of peptides from the N-terminal portion of αS1 casein, to irradiated mice receiving transplantation of limiting amounts of bone marrow, significantly enhanced platelet and leukocyte reconstitution (pages 83-84).

Yet further, clinical data in greater than 6 trials indicates that the administration of peptides from the N-terminal portion of αS1 casein both prior to, and following chemotherapy, stimulates platelet, erythrocyte, leukocyte proliferation, and prevented the characteristic depressed hematopoietic profile (see pages 92-95, and Figs 15, 16 and 17) found in chemotherapy recipients.

Thus, Applicant is of the strong opinion that the instant specification teaches the prevention, as well as treatment, of hematopoietic disorders such as thrombocytopenia, pancytopenia and granulocytopenia.

The abovementioned notwithstanding, and in order to further expedite prosecution in this case, Applicant has elected to amend claims 53, 57, and 61 to now recite: "A method of treating..." rather than "A method of preventing and treating...".
In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 13-64 and 97-100 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiners rejections are respectfully traversed. Claims 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 53, 54, 57, 58, 61, 62, 97, and 98 have now been amended. New claims 284-297 have been added.

With respect to claim 13, and claims 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61 and 97 the Examiner points out that the phrase "peptide derived from the N-terminus portion of oS1" is unclear as to the identity of "oS1 casein" and that the identity of "a peptide derived from oS1 casein" is also unclear from the instant specification.

Applicant regrets the unnecessary confusion associated with the typographical error in the designation of αS1 casein in the instant specification, and believes that the relevant comments and explanations provided hereinabove [see ***Specification/Claim Objections,*** item (3), and ***35 U.S.C. § 112, First Paragraph, Rejections***] have now clarified the identity of "oS1 casein" as "αS1 casein", and indicated the recitation of the full length sequence of the αS1 casein in the instant specification. Thus, as the amino acid sequence of αS1 casein, and of any defined peptides derived therefrom is well known in the art, one of ordinary skill in the art would instantly recognize the full length amino acid sequence of the N terminus of αS1 casein, and any defined component peptides.

The Examiner has further stated that the term "a peptide derived from an N terminus portion of αS1 casein" is unclear. Regarding the phrase "a peptide derived from αS1 casein", Applicant wishes to point out that (a)the instant specification is clear as to the definition of "a peptide derived from an N terminus of αS1 casein":

"As used herein the phrase "derived from an N terminus portion of αS1 casein" refers to peptides as this term is defined herein, e.g., cleavage products of αS1 casein (referred to herein as peptides derived from natural casein), synthetic peptides chemically synthesized to correspond to the amino acid sequence of an N terminus portion of αS1 casein (referred to herein as synthetic peptides derived from casein), peptides similar (homologous) to an N terminus portion of αS1 casein..." (page 34).

Thus, "peptides derived from casein" is defined as casein peptides representing a sequence corresponding to a portion, and not the entirety, of the amino acid sequence of the N-terminal portion of αS1 casein, of natural or synthetic origin, resulting from either cleavage of the αS1 casein polypeptide (as described, for example, on page 57, ***Materials and Experimental Methods***), or from chemical or enzymatic synthesis of such a peptide. Specifically, the Examiner has yet further stated that the phrase "a peptide derived from an N terminus portion of αS1 casein" is unclear as to whether or not said peptide has been isolated or purified from naturally-occurring casein and/or modified casein and/or synthesized casein. Applicant wishes to point out that inasmuch as "oS1 casein" has been identified as " αS1 casein", and the amino acid sequence of the αS1 casein N-terminus polypeptide is provided (see above, and page 34), one of ordinary skill in the art would instantly recognize peptides derived from the N-terminus portion of αS1 casein by their respective amino acid sequences, independent of their origin (from naturally occurring or synthetic casein, an αS1 casein peptide homologue, or a modified and/or synthetic casein).

Further, the Examiner has stated that dependent claims 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 100 are drawn to non-elected species. Please note Applicant's traversal of the additional election, brought hereinabove (see *Election/Restrictions*).
Still further, Applicant has now provided new independent claims 284-297, depending from independent claims 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61 and 97, including the limitation of:

"wherein said peptide has a sequence as set forth in SEQ ID NO: 4."

Thus new claims 284-297 read on methods for induction of hematopoiesis, megakaryocytopoiesis, granulocytopoiesis, etc, and treatment of related diseases, by administering the αS1 casein-derived peptide as set forth in SEQ ID NO: 4. No new material has been introduced.

Yet further, the Examiner has stated that in claim 94, "the effect of thrombopoietin" is not made clear. Applicant wishes to point out that the humoral factor thrombopoietin has been identified as a key factor in the development of a variety of blood cells and blood progenitor cells (see pages 4 and 5 of the instant specification), and as such, is widely considered a hematopoietic factor. In order to further clarify the method of the invention as taught in claim 94, Applicant has elected to amend claim 94 to

include the limitation "a hematopoietic effect of thrombopoietin", thus further defining the effects of thrombopoietin. Support for such an amendment is found, for example, on page 4, line 24 to page 5, line 5 of the instant specification:

"...it has been demonstrated that TPO is an early acting cytokine with important multilineage effects: TPO alone, or in combination with other early acting cytokines, can (i) promote viability and suppress apoptosis in progenitor cells; (ii) regulate hematopoietic stem cell production and function; (iii) trigger cell division of dormant multipotent cells; (iv) induce multilineage differentiation and (v) enhance formation of multilineage colonies containing granulocytes, erythrocytes, macrophages, and megakaryocytes (MK, CFU-GEMM). Moreover, TPO stimulates the production of more limited progenitors for granulocyte/monocyte, megakaryocyte and erythroid colonies, and stimulates adhesion of primitive human bone marrow and megakaryocytic cells to fibronectin and fibrinogen."

Further, while reducing the present invention to practice, a distinct synergy was observed between the effect of peptides derived from the N terminus portion of αS1 casein, and of thrombopoietin, on hematopoietic processes (megakaryopoiesis) (see pages 80-81, and the Table in Fig. 6).

In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 112, second paragraph, rejections.

35 U.S.C. § 102 Rejections – Enomoto et al (Mol Immunol 1990;27:581-586)

The Examiner has rejected claims 13-64 and 97-100 under 35 USC § 102 as being anticipated by Enomoto, et al. The Examiner's rejections are respectfully traversed. Claims 13, 14, 16-18, 20-22, 24-26, 28-30, 32-34, 36-38, 40-42, 44-46, 48-50, 52-54, 56-58, 60-62, 64, 97, 98 and 100 have now been amended.

The Examiner has stated that Enomoto et al. teaches that administration of a peptide representing amino acids 16-35 of αS1 casein stimulates T-cell proliferation (Figs. 2 and 3), and that such a peptide comprises the residues RPKHP, as set forth in SEQ ID NO: 4, thus anticipating claims 13-64 and 97-100. It is Applicant's belief that the Examiner has misinterpreted the teaching of the prior art, and that the cited reference is irrelevant to the teachings of instant claims 13-64 and 97-100.

Enomoto et al is a study of the T- and B- cell determinants on the αS1 casein polypeptide, using the technique of overlapping synthetic peptides, in order to identify potential immunogenic portions of αS1 casein. The amino acid sequence of αS1 casein, as used in the context of Enomoto et al, represents the processed αS1 casein, consisting of 199 residues (see Fig. 1, page 582, Table 1, page 583, and Table 2, page 585). Overlapping peptides of 19 or 20 residues were synthesized to cover the entire sequence of the mature αS1 casein polypeptide (page 582, left column). However, the αS1 casein polypeptide does not include the signal sequence "MKLLILTCLV AVALA" found in residues 1-15 of the unprocessed precursor of αS1 casein (see, for example, UNiProt/SwissProt Accession No. P02662).

Thus, contrary to the Examiner's assertion, the peptide referred to as "16-35" in Enomoto et al in fact does not, and cannot comprise the sequence "RPKHP", as set forth in SEQ ID NO:4, which represents amino acids 1-5 of the mature, processed αS1 casein, and as such, cannot and does not anticipate any of claims 13-64 and 97-100.

Further, Enomoto et al teach that peptide 1-20, which, by definition does include the sequence "RPKHP", is devoid of any immunogenic activity in the B- and T-cell assays disclosed (see Figs 2 and 3, page 583, and Table 2, page 585). Thus, Enomoto et al teaches away from the hematopoietic-inducing properties of SEQ ID NO: 4, as defined in the instant specification.

Thus, it is Applicant's strong opinion that the overlapping N-terminal casein peptides taught by Enomoto et al were not intended to, and cannot be used for inducing hematopoiesis and thus the teachings of Enomoto et al do not anticipate or render obvious the present invention.

Provisional Rejection- Obviousness Type Double Patenting

The Examiner has rejected claims 13-64 and 97-100 of the instant application on the basis of obviousness-type double patenting as being in conflict with claims 7, 9-11, 14-18, 39 and 41-43 of Application No. 10/788400, to the same inventor. In compliance with 37 CFR 1.321 (c), and as suggested by the Examiner, a terminal disclaimer, drafted and signed as set forth in 37 CFR 1.130(b), is attached herewith, thus overcoming the rejection on the basis of non-statutory double patenting.

In view of the above remarks it is respectfully submitted that claims 1,3-64, 97-100 and new claims 284-297 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Martin Moynihan
Registration No. 40,338

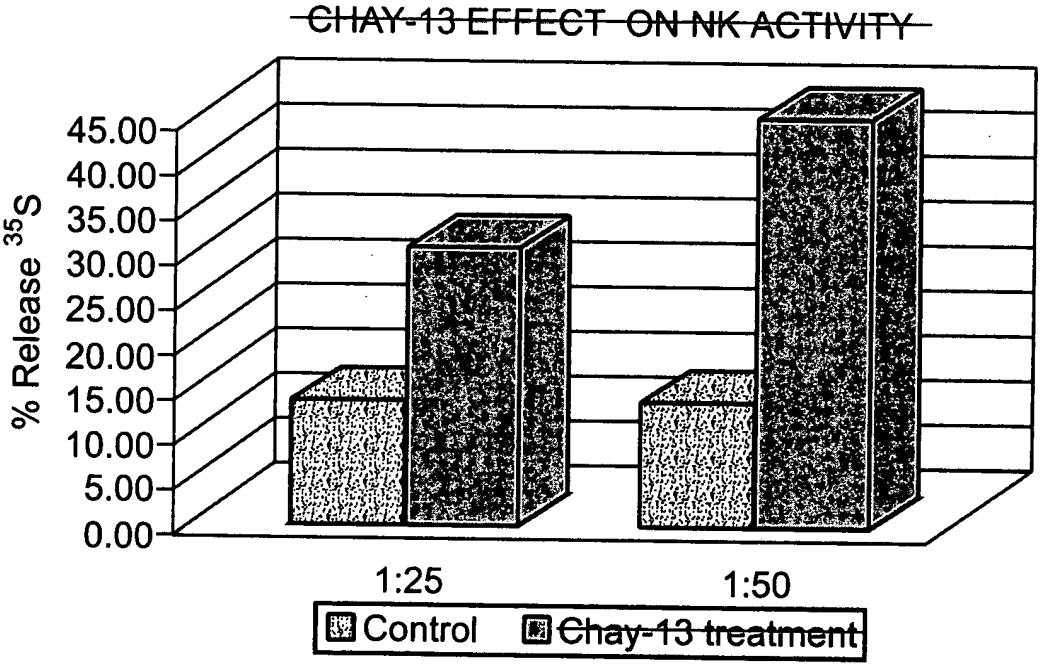
Date: November 29, 2005

Enclosures:

A Petition and Fee for Extension of Time;
A Response Transmittal Fee For Added Claims;
A Terminal Disclaimer In Compliance With 37 CFR 1.130(b);
Letter To Chief Draftsman;
14 Sheets Of Annotated Marked-Up Drawings;
Formal Drawings Transmittal Sheet;
21 Sheets Of Formal Drawings

~~Peptides Derived from Natural Casein Stimulate Murine Natural Killer (NK) Cell Activity~~

~~Group ->~~	~~1:25~~		~~1:50~~	
~~Ex. No v~~	~~Control~~	~~Chay-13~~	~~Control~~	~~Chay-13~~
~~1~~	~~16.10~~	~~43.80~~	~~27.50~~	~~62.80~~
~~2~~	~~25.70~~	~~45.40~~	~~18.20~~	~~43.40~~
~~3~~	~~0.00~~	~~3.10~~	~~0.00~~	~~35.00~~
~~4~~	-	-	~~9.00~~	~~35.00~~
~~Average~~	~~13.93~~	~~30.77~~	~~13.68~~	~~44.05~~
~~SD~~	~~12.99~~	~~23.97~~	~~11.84~~	~~13.11~~



PEPTIDES DERIVED FROM NATURAL CASEIN TREATMENT

Fig. 1

~~Effect of Peptides Derived from Natural Casein on Human Natural Killer (NK) Cell Activity in Cells from a Single Donor~~

Dose>	0	5	10	25	50	100	250	500
1:50	3.9	5.4	11.3	10.9	9.1	8.3	12.5	15.5
1:100	4.6	5.1	12.4	12.8	11.9	10.8	12.1	14.9

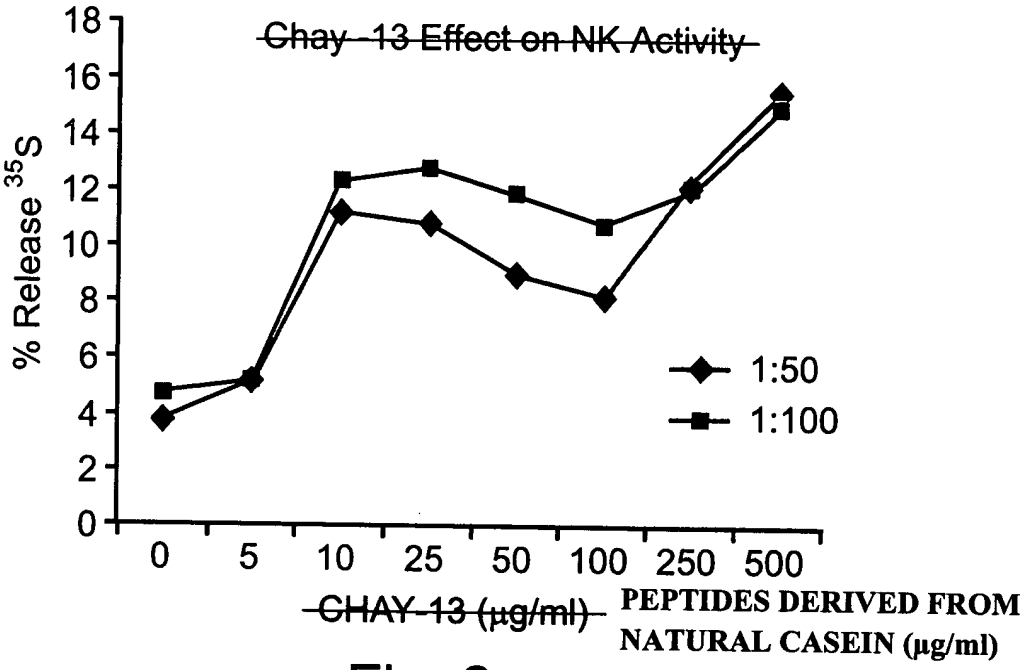


Fig. 2a

Selective Stimulation of Human Natural Killer (NK) Cell Activity by Peptides Derived from Natural Casein

Patient	Type	0	10	25	100	250	500
1	Normal	13	15	15	12	13	15
2	NHL	10.1	13.8	14.3	-	15.8	13.7
3	NHL	3.5	10.4	8.4	10.8	-	-
4	Br. Ca.	4.2	2.7	7.1	7.7	5.9	10.1
5	-	12.2	18.1	19.1	14.3	13.4	15.8
6	-	17	15	15	15	13	9

Fig. 2b

Peptides Derived from Natural Casein Stimulate Proliferation of Human CD_{56} Surface Antigen Positive (NK) Cells

	NK CELL PROLIFERATION % $FLCD_{56}$	
Patient	Control	~~Chay-13~~
1	0.60	0.20
2	0.60	1.90
3	0.10	0.90
4	0.40	3.30
5	1.50	3.70
Mean	0.64	2.00
SD	0.52	1.50

PEPTIDES DERIVED FROM NATURAL CASEIN

EFFECT OF PEPTIDES DERIVED FROM NATURAL CASEIN

~~EFFECT OF CHAY-13~~ ON NK PROLIFERATION

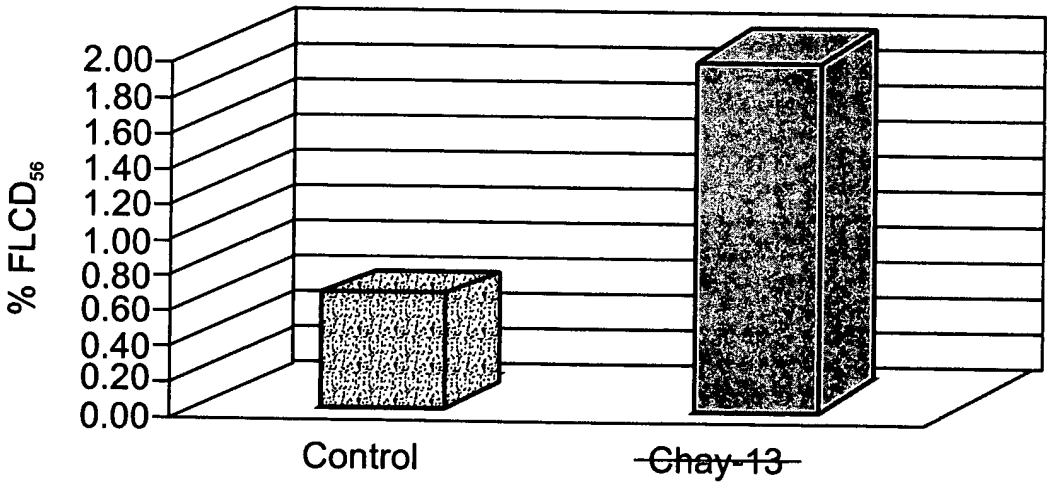


Fig. 3a

Peptides Derived from Natural Casein Stimulate Proliferation of Human CD_3 Surface Antigen Positive (T) Cells

	NK CELL PROLIFERATION % $FLCD_3$	
Patient	Control	~~Chay-13~~ PEPTIDES DERIVED FROM NATURAL CASEIN
1	7.90	10.40
2	8.19	10.46
3	12.82	58.64
4	62.86	50.44
5	5.49	47.76
Mean	19.45	35.54
SD	24.41	23.27

EFFECT OF PEPTIDES DERIVED FROM NATURAL CASEIN

~~EFFECT OF CHAY-13~~ ON T CELL PROLIFERATION

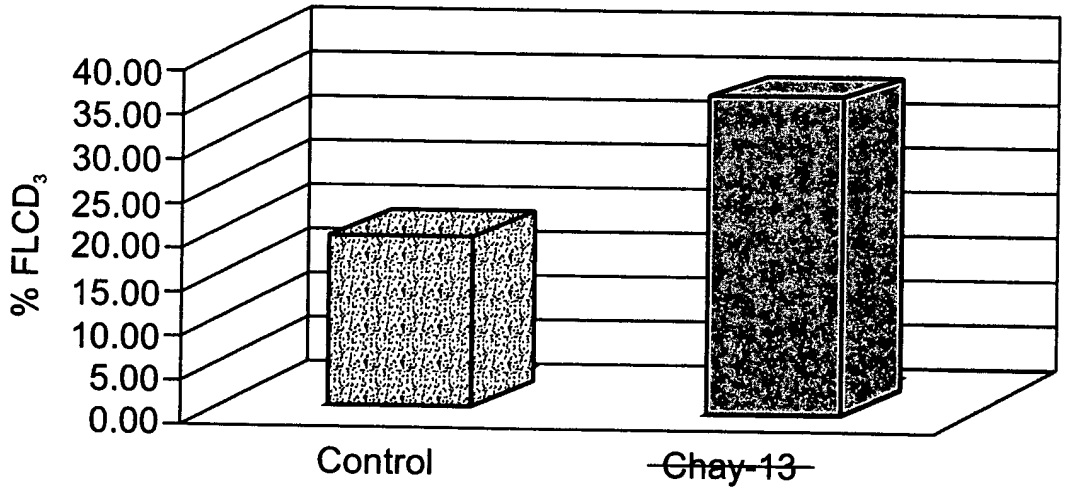


Fig. 3b

Peptides Derived from Natural Casein Stimulate Proliferation of Human CD_{56} and CD_3 Surface Antigen Positive (NK/T) Cells

NK CELL PROLIFERATION % $FLCD_3/FLCD_{56}$

Patient	Control	~~Chay-13~~
1	8.00	25.00
2	1.1	4.3
3	0.1	0.85
4	2.77	3.89
5	1.74	4.34
6	0.84	4.53
7	0	2.55
Mean	2.08	6.49
SD	2.78	8.27

PEPTIDES DERIVED FROM NATURAL CASEIN

EFFECT OF PEPTIDES DERIVED FROM NATURAL CASEIN

~~EFFECT OF CHAY-13~~ ON PBSC PROLIFERATION

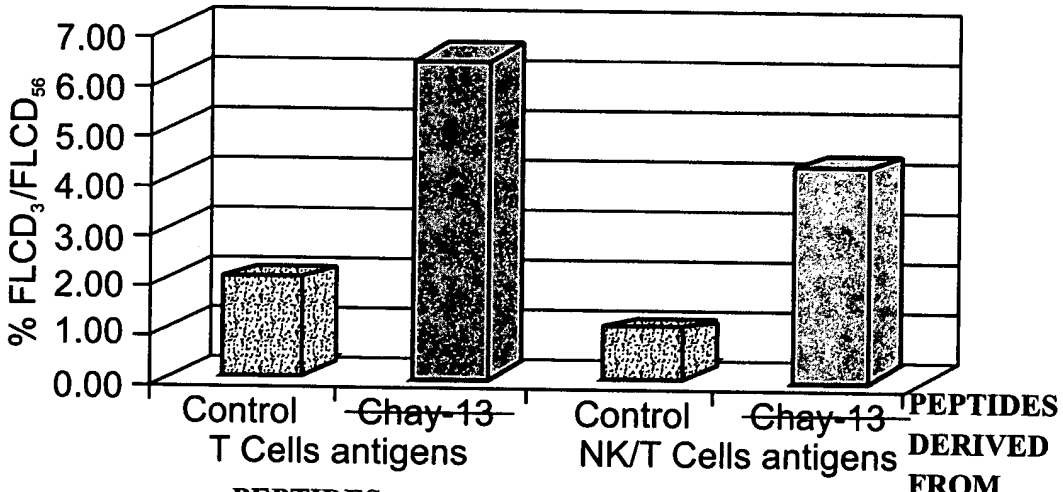


Fig. 3c

~~The Effect of Synthetic Peptides on the Stimulation of NK Cells Activity in Cultured Human PBC~~

~~PEPTIDE~~	NK CELLS ACTIVITY (%^{35}S RELEASE)										
	0µg/ml	10 µg/ml		25µg/ml		100 µg/ml		250 µg/ml		500 µg/ml	~~ug/ml~~
PEPTIDE 1a SEQ ID 9	4.3 %	1880	7.3%	1803	6.2%	2006	9.2%	1761	5.6%	1768	5.6% ~~1a~~
PEPTIDE 2a SEQ ID 10	4.3 %	1762	5.6%	1908	7.7%	1840	6.7%	1805	6.2%	1883	7.4% ~~2a~~
PEPTIDE 3a SEQ ID 11	4.3 %	2003	9.1%	1868	7.1%	1847	6.8%	1671	4.2%	1997	9.1% ~~3a~~

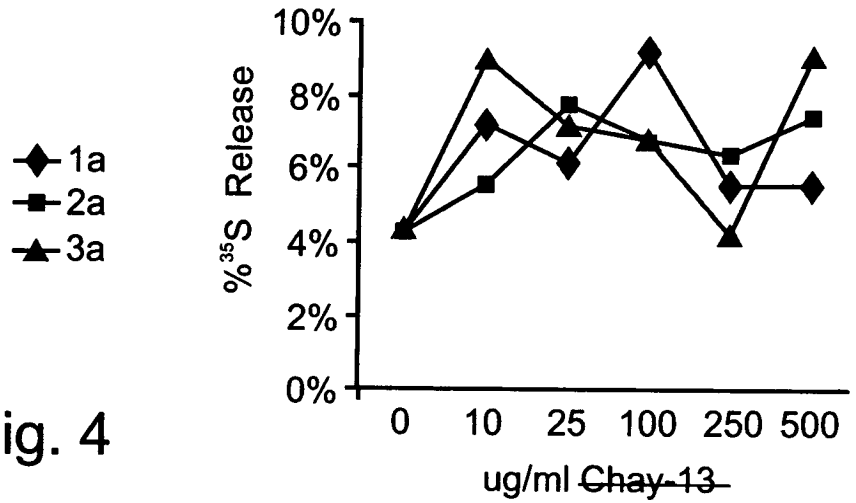


Fig. 4

SYNTHETIC PEPTIDES DERIVED FROMαS1 CASEIN

STEM CELL PROLIFERATRION (T^3H)	
	PEPTIDES DERIVED FROM NATURAL CASEIN

~~Peptides Derived from Natural Casein Stimulate Proliferation of Cultured Human Peripheral Blood Stem Cells~~

Blood origin	Incubation period (days)	Control	50 (µg/ml)	100 (µg/ml)	300 (µg/ml)	600 (µg/ml)
PBSC	20	1663	3007	1800	4306	3310
PBSC	15	741	1612	784	-	920
BM normal	21	675	-	660	834	817
BM Auto	21	945	-	916	1537	1284
BM 1	21	1829	4217	4396	9178	1446
BM 2	21	1829	5039	2939	1496	-
CB1	14	1159	1191	1694	3961	3297
CB2	14	3434	-	10882	-	13560

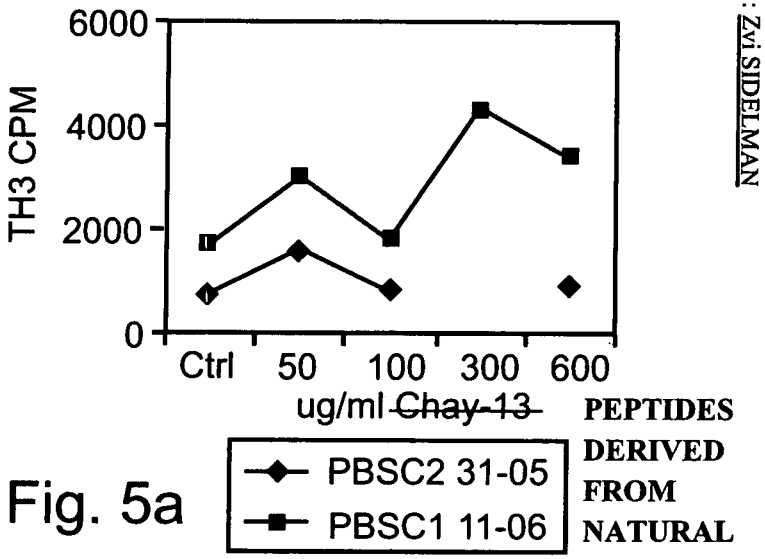


Fig. 5a

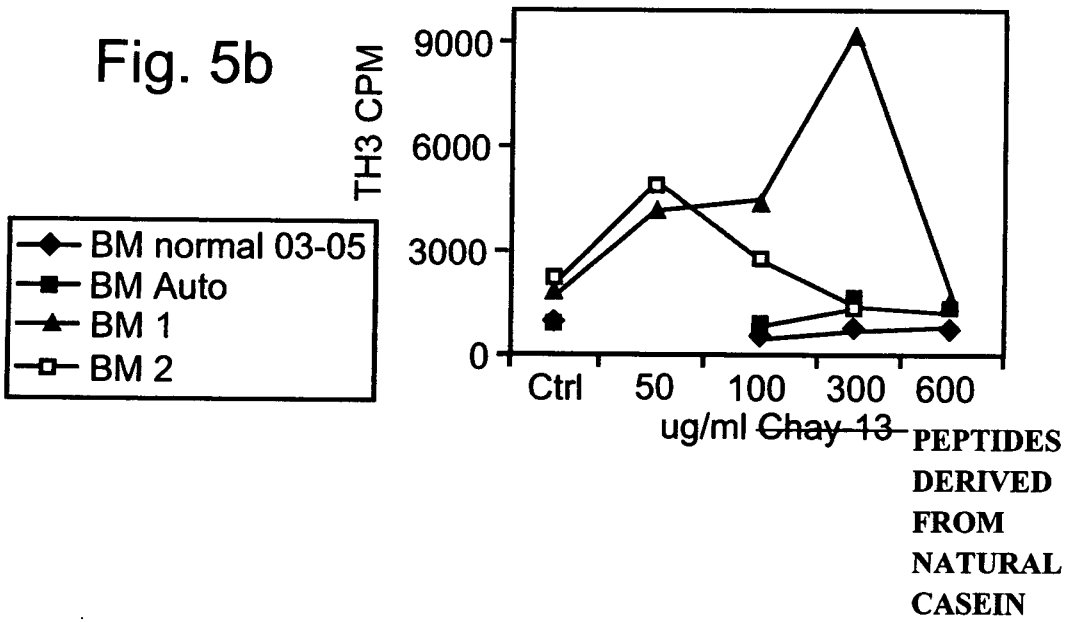


Fig. 5b

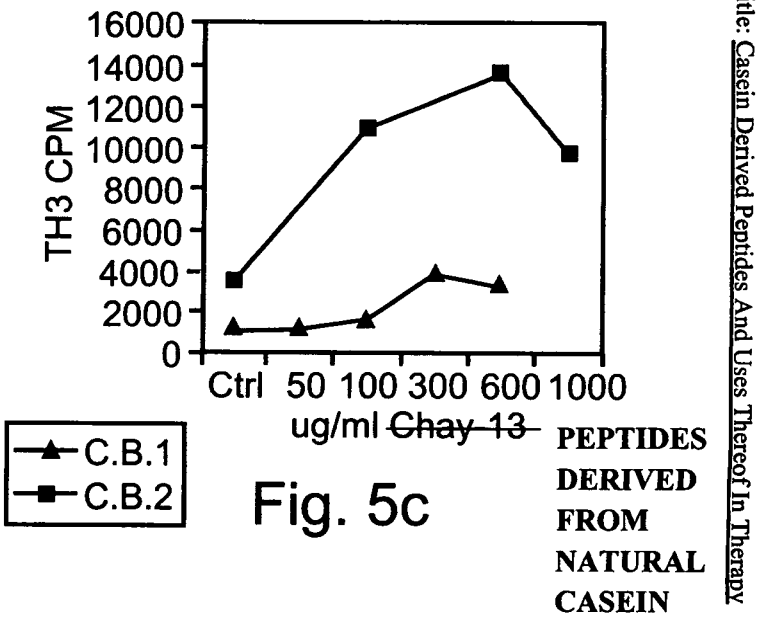


Fig. 5c

Serial No.: 09/942,121
Inventor : Zvi SIDELMAN

ANNOTATED MARKED-UP SHEET

Title: Casein Derived Peptides And Uses Thereof In Therapy

Sheet: 7 of 14

Peptides Derived from Natural Casein Stimulate Proliferation of Normal Human Hematopoietic Cells

Donor	Days Of Incubation	Factors Added	Relative Cell No. X 104/ml μg ~~Chay-13~~/ml PEPTIDES DERIVED FROM NATURAL CASEIN				
			0	25	100	250	500
Bone Marrow	14	EPO, hIL-3, hSCF,AB serum	41	64	-	67	51
Cord Blood	13	EPO, hIL-3, hSCF,AB serum	27	158	66	50	-

Fig. 6

Peptides Derived from Natural Casein Stimulate Leukoctye Proliferation in Irradiated, Bone Marrow Reconstituted Balb Mice.

Days After Treatment	2		4		6		9		12		15	
	Control	Chay-13	Control	Chay-13	Control	Chay-13	Control	Chay-13	Control	Chay-13	Control	Chay-13
1	6	9	6	32	55	55	90	205	100	280	500	800
2	10	10	18	34	40	45	135	100	160	280	440	540
3	4	6	14	40	20	85	100	130	140	220	380	800
4	6	6	8	14	35	58	130	125	280	440	600	640
5	12	6	16	18	75	60	70	155	40	340	520	600
6	8	10	18	90	25	45	85	90	320	160	380	640
Mean	7.67	7.83	13.33	38*	41.67	58*	101.67	134.17	173.33	286.67	470	670
SD	2.69	1.86	4.71	24.95	18.63	13.42	23.57	38.01	97.75	88.44	78.95	97.81

* p<0.008

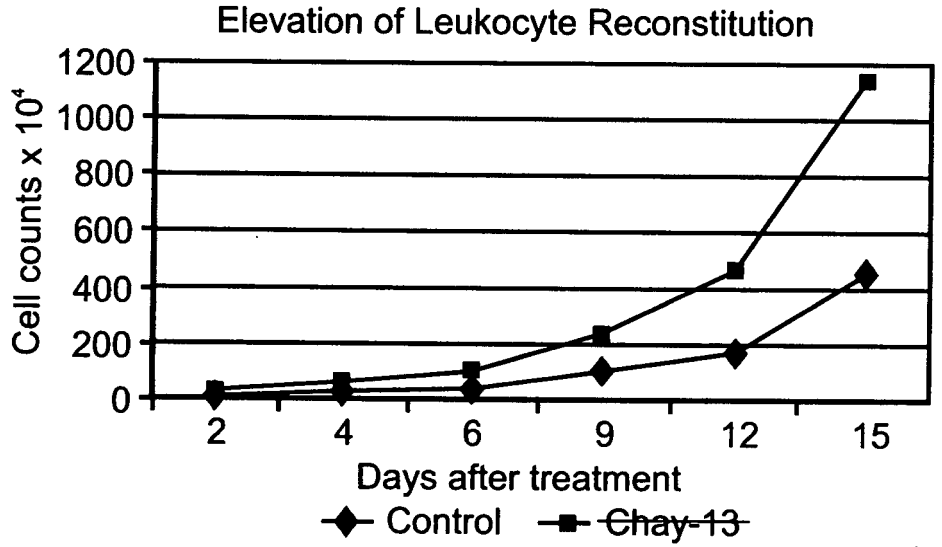


Fig. 8

1 MG PEPTIDES DERIVED FROM NATURAL CASEIN

Peptides Derived from Natural Casein Stimulate Thrombocyte Proliferation in Irradiated, Bone Marrow Reconstituted CBA Mice.

THROMBOCYTE PROLIFERATION (PLT X 10^3)

Days After Treatment	DAYS AFTER 11 TREATMENT		DAYS AFTER 13 TREATMENT		DAYS AFTER 15 TREATMENT	
	Control	~~Chay-13~~	Control	~~Chay-13~~	Control	~~Chay-13~~
1	43	50	75	103	98	110
2	48	54	71	105	99	128
3	68	68	80	110	102	111
4	64	64	104	104	96	103
5	67	67	91	101	104	133
6	63	54	90	90	97	114
7	54	45	104	107	87	104
8		63		104		116
9		61		93		115
10		57		116		112
Mean	58.14	58.3	87.86	103.3*	97.57	114.6**

PEPTIDES DERIVED FROM NATURAL CASEIN

PEPTIDES DERIVED FROM NATURAL CASEIN

PEPTIDES DERIVED FROM NATURAL CASEIN

* $p<0.01$ ** $p<0.0001$

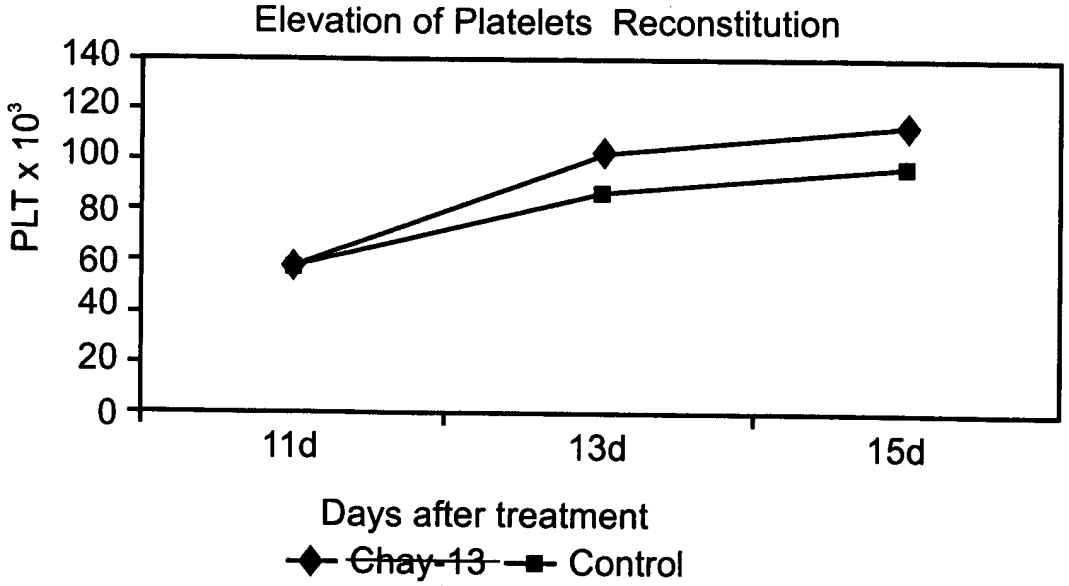


Fig. 9

Stimulation of Sup-T_1 Lymphocyte Cell Proliferation by Peptides Derived from Natural Casein

PEPTIDES DERIVED FROM NATURAL CASEIN

~~Chay 13~~ μ g/ml	3 days		7 days	
	cpm Counts	Proliferation Index	cpm Counts	Proliferation Index
50	9268	1.18	120954	1.10
100	9940	1.26	112436	1.02
300	8425	1.07	102957	0.93
600	9771	1.24	101987	0.93
1000	8390	1.06	86649	0.79
Control	7862		109560	

PEPTIDES DERIVED FROM NATURAL CASEIN

~~Chay 13~~ μ g/ml	10 days		14 days	
	cpm Counts	Proliferation Index	cpm Counts	Proliferation Index
50	17695	1.03	22272	1.36
100	19168	1.12	22842	1.40
300	21806	1.28	15318	0.93
600	22826	1.34	17368	1.06
1000	21764	1.28	10034	0.61
Control	17046		16313	

Fig. 11

Peptides Derived from Natural Casein Inhibit of HIV-1 Infection of CEM Cells: Cell Proliferation vs.P^{24} Antigen Levels

PEPTIDES DERIVED FROM NATURAL CASEIN	~~Chay 13~~ µg/ml	CEM cells	
		Cell No. ($x10^6$) 15 days	P^{24}Ag ng/ml
3H	50	0.29	16.39
	100	0.55	7.73
	300	0.54	1.61
	600	0.75	0.18
	1000	0.57	0.19
24H	50	0.40	0.24
	100	0.48	4.21
	300	0.56	2.94
	600	0.62	0.18
	1000	0.79	4.03
48H	50	0.37	10.05
	100	0.50	9.16
	300	0.56	3.21
	600	0.70	16.49
	1000	0.84	2.16
Control	IF	0.35	11.42
	UIF	0.42	0.17

Fig. 12

Peptides Derived from Native Casein Stimulate Thrombocytopoiesis in Acute Myeloid Leukemia (Patient M-1)

X	Y
0	11
1	10
3	10
5	32.5
7	15
8	27.5
12	40
14.25	28
17	35
21	45
26.35	70.3
31.7	74
40	100.7

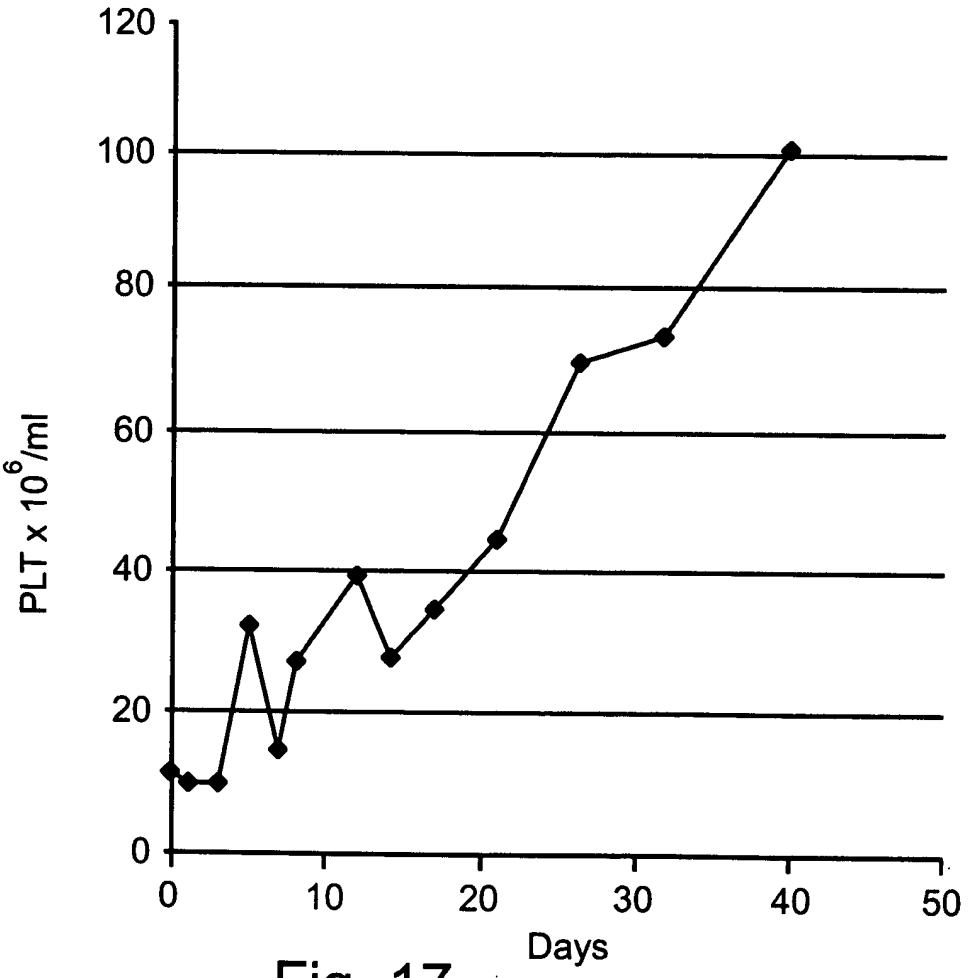


Fig. 17

X	Y
0	23
1	18.5
2	25
3	16
4	20.8
6	20.8
7	20
8	23.5
9	26
10	19.5
11	23
13	18.5
14	18.5
15	20
17.2	22
20.3	30
24	44
29	75.6
36.5	86.4
41	139.5

Peptides Derived from Native Casein Stimulate Thrombocytopoiesis in Acute Myeloid Leukemia (Patient M-2)

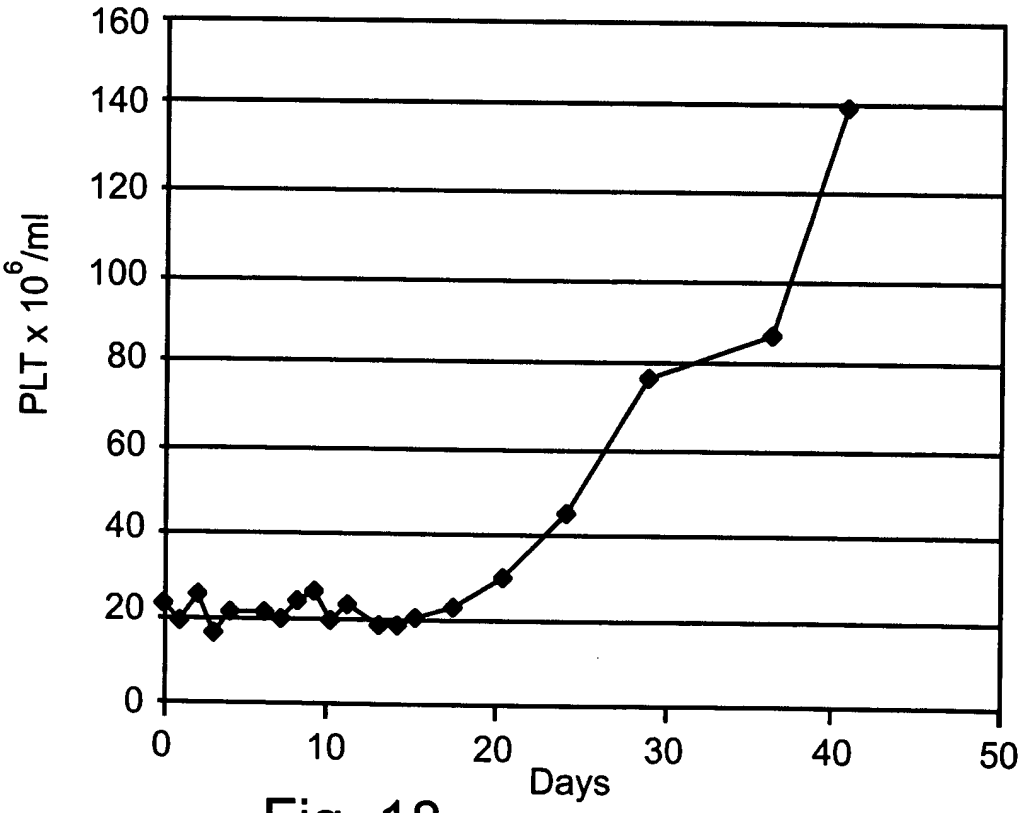


Fig. 18